Overview of Trichloroethylene (TCE) Occurrence and Regulatory Trends

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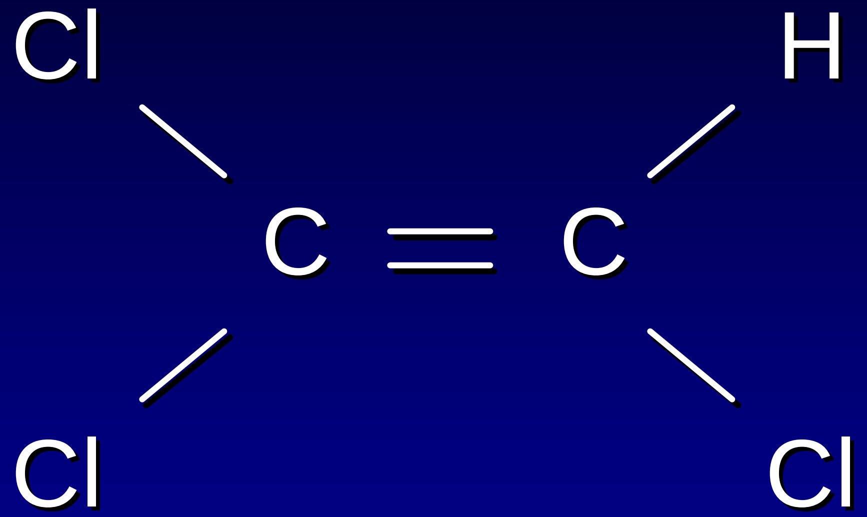
Trichloroethylene



(Trichloroethene; TCE; TRI)

Historical Uses of Trichloroethylene

- Medical uses
  - Anesthetic agent
  - Analgesic for trigeminal neuralgia
  - Disinfectant
- Extraction solvent for foods
- Solvent in manufacture of cosmetics
- Dry cleaning solvent

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Current Uses of Trichloroethylene

- Metal degreasing agent
- Manufacturing solvent
  - Pesticides
  - Varnishes, lacquers, paints
  - Dyes
- Component of
  - Adhesives
  - Spot removers
  - Rug cleaners
  - Disinfectants

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Why should TCE be evaluated?

- Occupational exposures
- Environmental contaminant
  - Widespread
  - Persistent
  - Mobile

Conflicting Evaluations of Health Risks from TCE Exposure

- IARC: 2A - Probable Human Carcinogen
- ACGIH: A5 - Not Suspected to be a Human Carcinogen – under occupational scenarios
- NTP: Reasonably Anticipated to be a Human Carcinogen (Not Upgraded)
- EPA: Removed classification from IRIS 1986; re-evaluation pending; draft assessment (2001) concludes TCE is “highly likely to produce cancer in humans”

Decision Tree Method for Potential Carcinogens

- Does TCE damage DNA?
  - Bacteria
  - Mammalian cells
- Is exposure to TCE associated with elevated human cancers?
  - Target organs
  - Dose-related incidences
  - Consistency
- Does TCE cause cancer in animals?
  - Threshold
  - Similar metabolism in humans?

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Results of Genotoxicity Studies

- TCE and oxidative metabolites
  - Many in vitro and in vivo studies
  - Negative or weakly positive
- Reductive metabolites
  (via glutathione conjugation)
  - Positive
  - Not quantitatively important in humans

Epidemiology

- Study of the distribution and determinants of disease
- Identifies factors that
  - Differ between two populations
  - Are sufficiently important to play a determining role in the cause of a disease

Types of Epidemiology Studies

- Cluster analyses
  - Episodic observations of isolated disease cases, often related to exposure to an agent
- Case-Control Studies
  - Retrospective investigations of histories and habits of persons who developed a disease
- Cohort Studies
  - Longitudinal (prospective or retrospective) investigations of persons exposed to an agent

Criteria Used to Infer Causality

- Temporal relationship
- Strength of association
- Specificity of association
- Dose-response relationship
- Consistency
- Biological plausibility

Selected Case-Control Studies of TCE and Kidney Cancer

Cases	Controls	Exposure	Results & Comments	Reference
12 (Mass. transformer plant)	1202 (from same employer)	Work histories, job exposure matrix	Risk of kidney cancer ⟷	Greenland et al. (1994)
438 (Minn.)	687 (population)	Work histories, job exposure matrix	Risk of renal cell carcinoma ⟷ Gender difference?	Dosemeci et al. (1999)
935 (Germany)	4298 (population)	Job title/tasks, job exposure matrix	Risk of renal cell carcinoma ⟷ No evidence of gender difference	Pesch et al. (2000)
58 (Germany)	84 (hospital)	Work histories, interviews	OR 10.8 (3.36-34.75) for renal cell carcinoma High, long-term exposures Methodological flaws	Vamvakas et al. (1998)

Criteria for Inclusion of Cohort Studies in Further Analysis

- Investigation of cancer outcomes
- Cohort size of >750
- Assessment of TCE exposure
- Follow-up period of > 25 years

Selected Cohort Studies of TCE

Cohort	Size	Years	Exposure	Results & Comments	Reference
Hill AFB, UT	7204	38	Job titles/ descriptions, interviews, historical records	Cancer incidence ↔ Cancer mortality ↔ Kidney cancer incidence ↔ Kidney cancer mortality ↔	Blair et al. (1998)
Hughes Aircraft plant, AZ	4733	43	Job exposure matrix	Cancer mortality ↔ Kidney cancer mortality ↔ Healthy worker effect	Morgan et al. (1998)
Lockheed Martin aircraft plant, CA	2267	36	Job descriptions, interviews, historical records	Cancer mortality ↓ Kidney cancer mortality ↔	Boice et al. (1999)

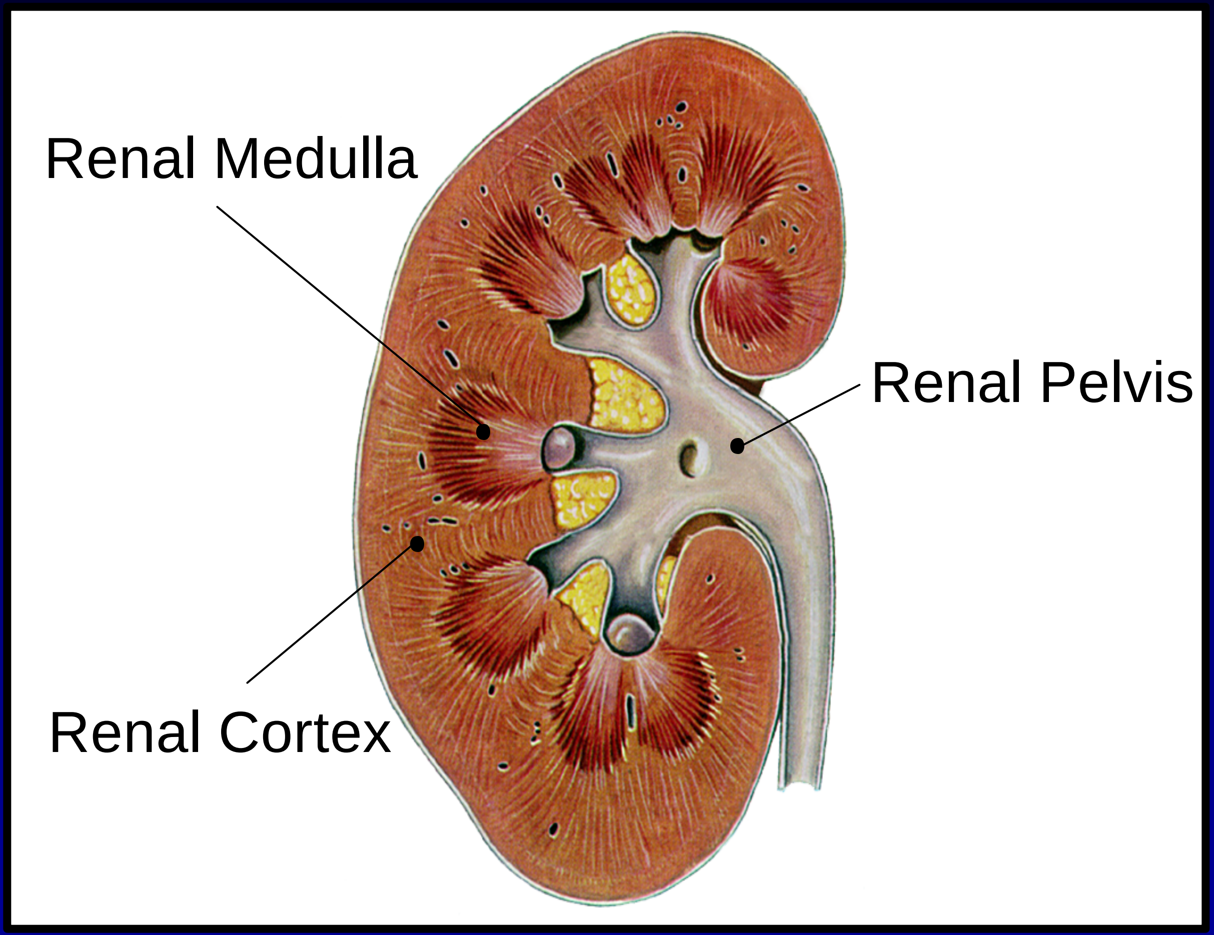
Selected Cohort Studies of TCE

Cohort	Size	Years	Exposure	Results & Comments	Reference
Swedish workers	1670	32	Urinary TCA	Cancer mortality • ↓ Cancer mortality • ↔ Kidney cancer incidence ↔	Axelson et al. (1994)
Finnish workers	3089	26	Urinary TCA	Cancer mortality ↔ Cancer incidence ↔ Kidney cancer incidence ↔	Anttila et al. (1995)
Danish workers	803	28	Air TCE, urinary TCA	Cancer incidence ↔ Kidney cancer incidence ↔	Hansen et al. (2001)
German cardboard factory	169	37	Job histories, interviews	Kidney cancer incidence ↑ 5-10x Kidney cancer mortality ↔ High, long-term exposures Methodological flaws	Henschler et al. (1995)

Some Cautions Regarding the Henschler Study

- Small cohort size (N = 169) limits statistical robustness
- Study emanated from a cluster
  - Formed the basis for the hypothesis
  - Purists would have excluded the cluster from a longitudinal study
- Unexposed cohort exhibited 9-fold increase in brain cancer deaths
  - Attributed to "observer sensitivity bias"

Sagittal Section of the Kidney



Some Cautions Regarding the Henschler Study

- Critics call attention to the mis-grouping of the renal pelvis tumor with renal cell tumors
  - Different location
  - Different tissue of origin
  - Recognized by the authors and deliberately done
- There is a lack of a dose-response
  - Three renal cell tumors in the low-exposure group; latency periods of 18-19 yr
  - One renal cell tumor and one renal pelvis tumor in the high-exposure group; latency periods of 34 yr

Assessment of Selected Epidemiology Studies

- Most data do not support an association between TCE exposure and kidney cancer in humans
  - Among selected case-control studies of TCE
    - 3 negative
    - 1 positive
  - Cohort studies which met inclusion criteria
    - 6 negative
  - One small, flawed cohort study positive

Chronic Inhalation Studies of Animals Exposed to TCE

- TCE at 0, 100, 300, 600 ppm
  7 hr/d, 5 d/wk, for 78 wk
  to Swiss and B6C3F1 mice
  - Male Swiss: dose-related lung and liver tumors
  - Female B6C3F1: dose-related lung tumors
- TCE at 0, 100, 300, 600 ppm
  7 hr/d, 5 d/wk, for 104 wk
  to Sprague-Dawley rats
  - Males: dose-related kidney toxicity and tumors
- Negative results in hamsters

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Chronic Oral Studies of Animals Exposed to TCE

- Early studies confounded by carcinogenic stabilizers
- TCE at 0 or 1000 mg/kg
  5 d/wk for 103 wk to B6C3F1 mice
  - Both sexes: increased liver tumors and kidney toxicity
- TCE at 0, 500, or 1000 mg/kg
  5 d/wk for 103 wk to 5 strains of rats
  - Inadequate for assessing carcinogenicity
  - Both sexes of all 5 strains: increased kidney toxicity
  - Males of 2 strains: increased kidney tumors

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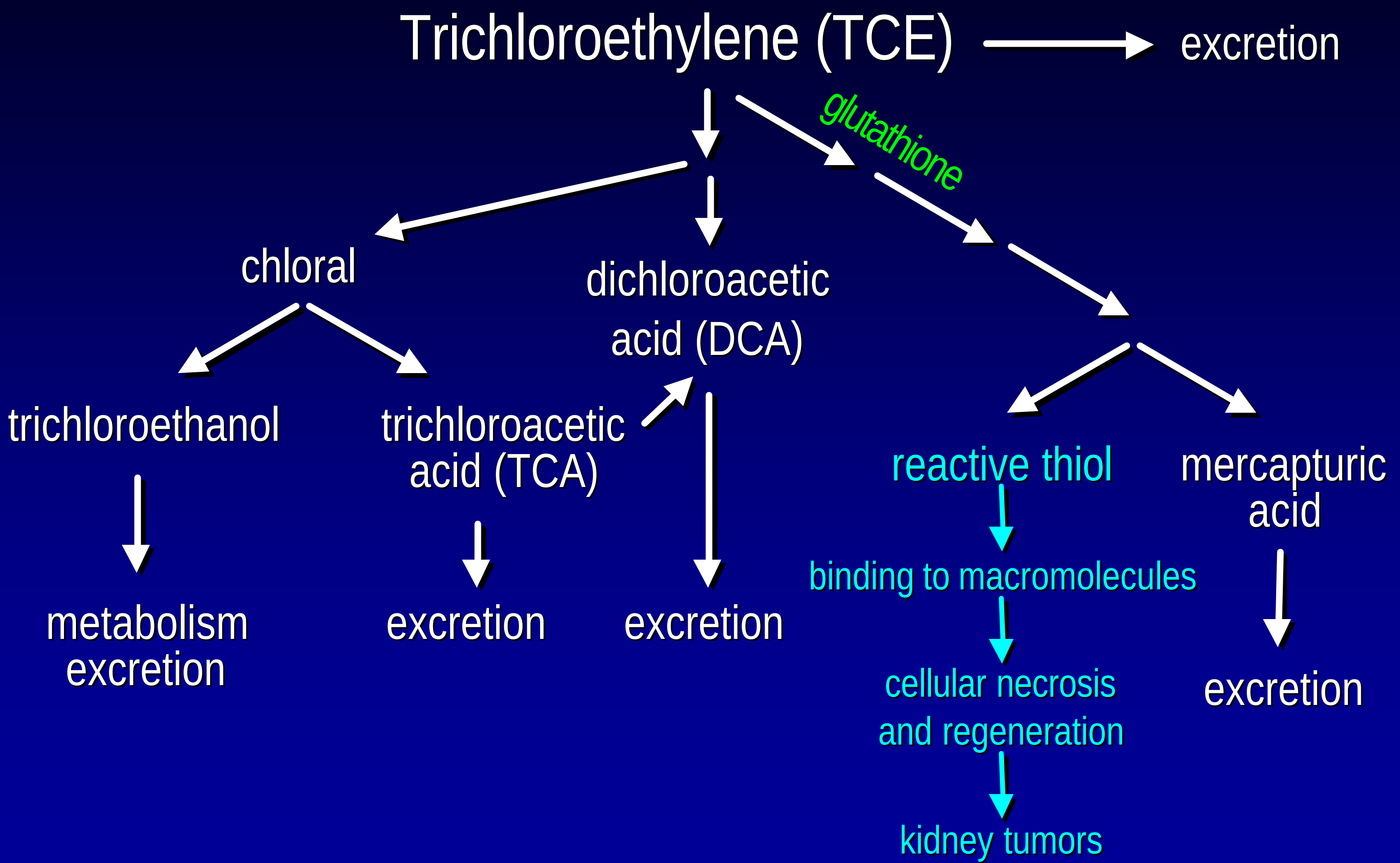
Metabolism of TCE



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Likely Mechanism for Renal Tumor Development in Rats

Chronic High Dose

Trichloroethylene → Kidney Necrosis → Regenerative Hyperplasia → Tumors

Chronic Low Dose

Trichloroethylene → No Obvious Changes in Tissues → Normal Tissues (No Tumors)

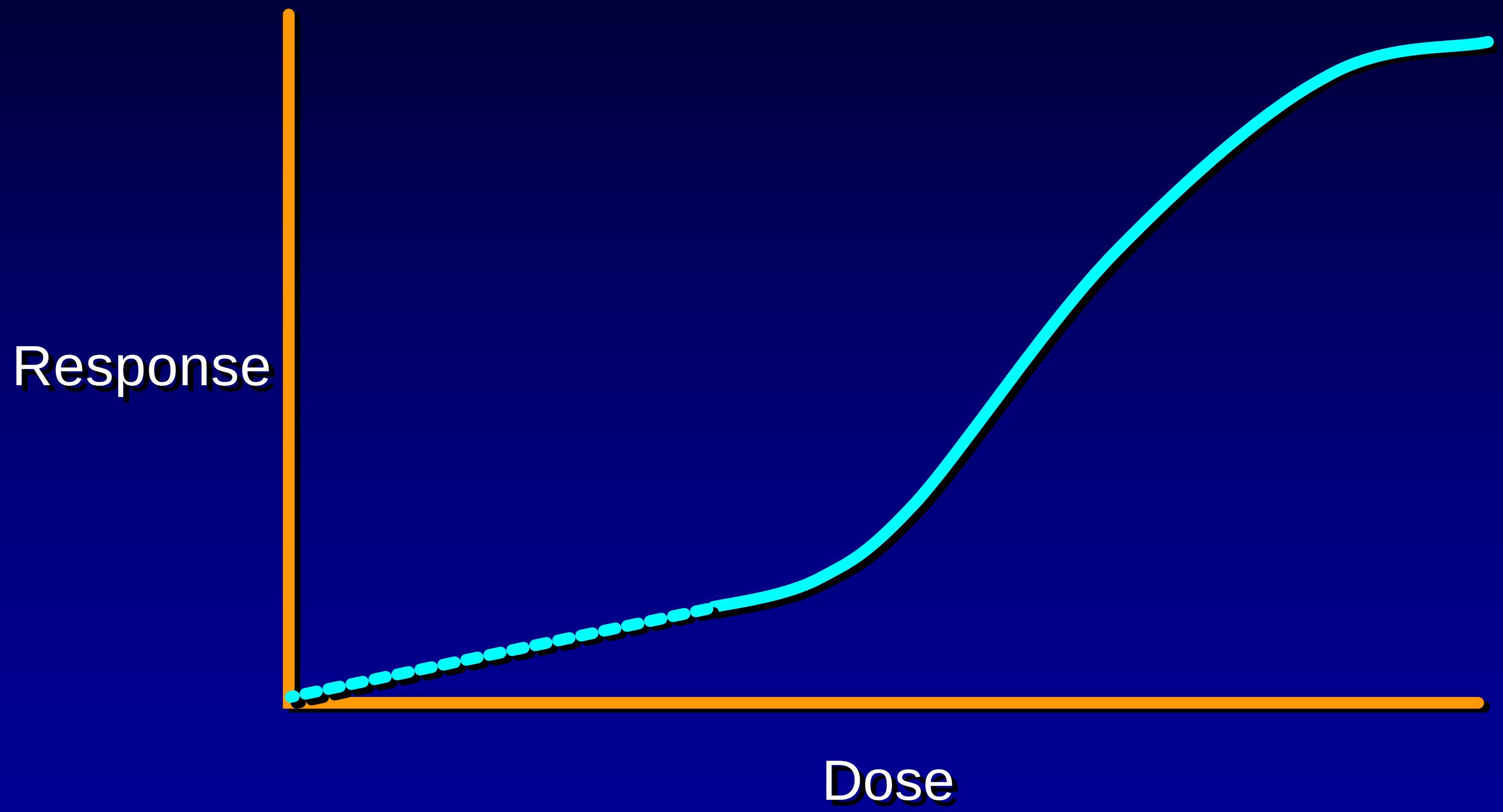
Status of the Carcinogenicity Issue

- Qualitative and quantitative differences exist between rodent and human metabolism of TCE.
- Rodent tumors develop only at high doses of TCE.
- A threshold exists for TCE-induced rodent tumor development based on chronic tissue damage and subsequent regeneration.
- TCE has not been associated consistently with human cancer or increased mortality.
- At low, environmental concentrations, TCE is not likely to be a human carcinogen.

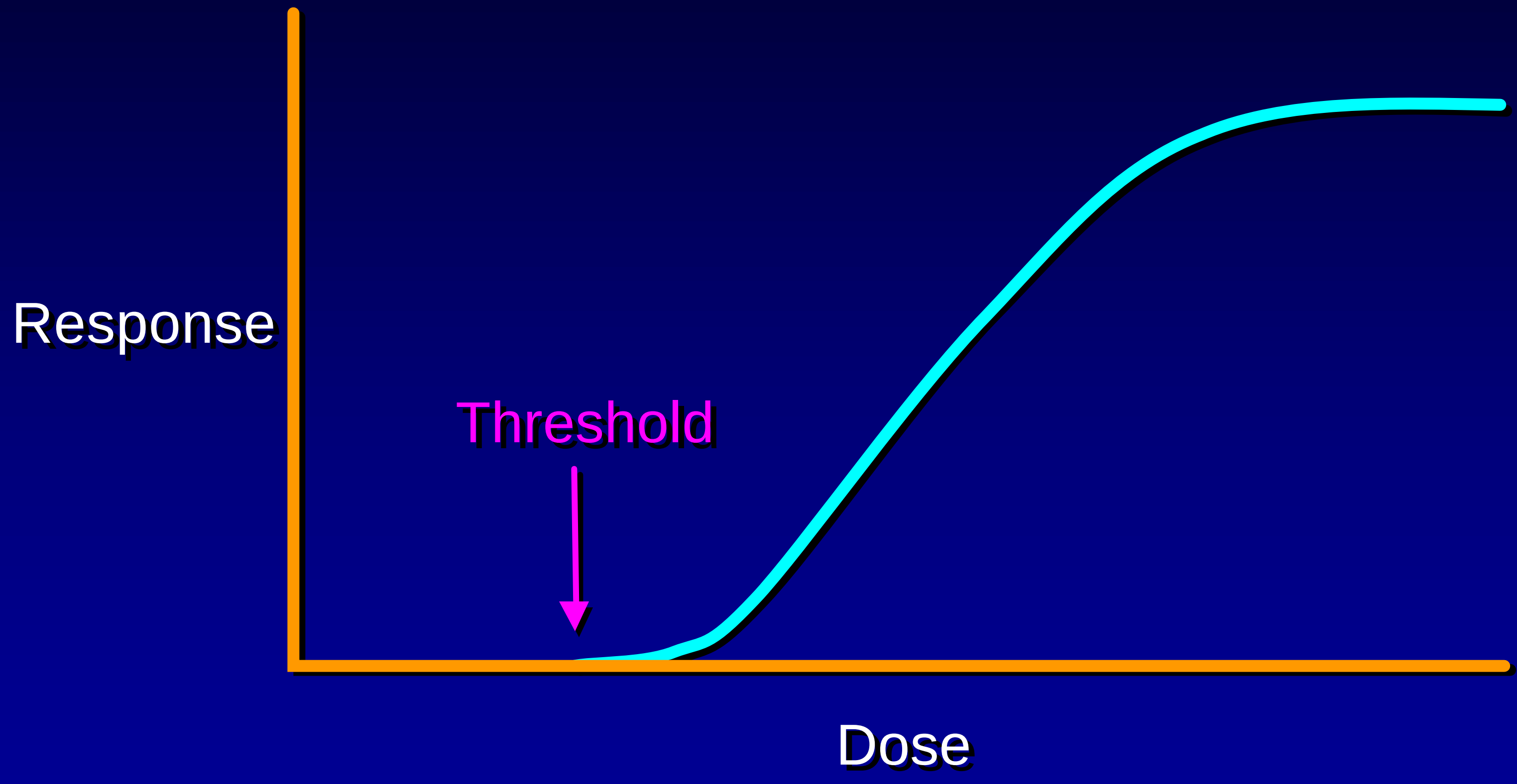
Bases for the EPA Position

- EPA relies heavily on the Henschler study because it alleges cancer outcome in humans
- Emerging concept of “opportunistic carcinogen” is being applied to TCE
- New molecular findings could be consistent with a possible cancer effect and speculations about non-cancer endpoints, suggesting the absence of a toxicity threshold
  - Unvalidated
  - Small numbers of subjects
  - Highly speculative
- Conservative (over-protective) position is easy to defend

Non-threshold Dose-Response Relationship



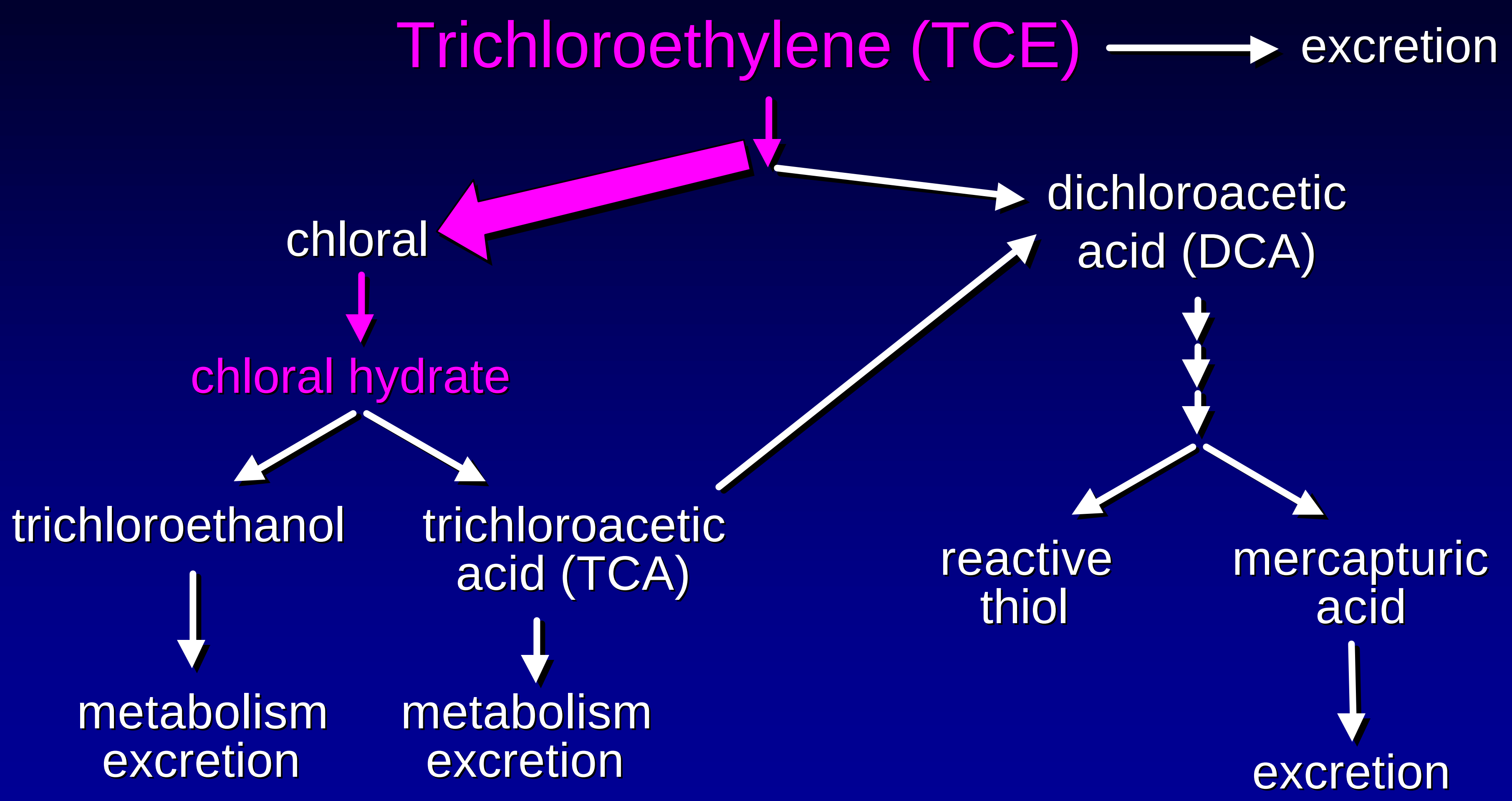
Threshold Dose-Response Relationship



Probable Consequences of EPA Assessment

- Maximum contaminant level (MCL) for drinking water will decrease
  - Likely range will be 0.3 – 1.0 µg/L (0.3 – 1.0 ppb)
- Closed sites may be re-examined and, potentially, re-opened
- Soil vapor intrusion into crawl spaces, basements, and buildings will result in new clean-up challenges

Metabolism of TCE in Humans



A Perspective on Amounts

- Pediatric dose of chloral hydrate = 900 mg
- How much water is required to dilute this to the current MCL of TCE (5 μg/L)?
  - ~42,500 gallons
  - A swimming pool 40' long x 20' wide x 8' deep
- At 2 L/day, how long for a single person to drink it all?
  - Over 245 years
  - (At 1 μg/L, it would take over 1200 years)

Points to Remember

- MCLs are ***not*** clean-up standards
- Site-specific risk assessments will be important and should be conceptualized early
- It is incumbent on remedial investigation personnel to carefully determine future uses of land and aquifers
  - Future use should guide what clean-up method should be used and what the clean-up standard should be
- Well head treatment may prove to be the most efficient and cost effective strategy

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